Appendix

This appendix provides additional details for the study of long-acting opioids and should be read in conjunction with the primary manuscript (MS).

1. Cohort

All study data were obtained from Tennessee Medicaid files, an efficient data source for identifying the cohort, determining periods of probable exposure to medications, and ascertaining deaths.[1;2] The study Medicaid database included enrollment, pharmacy, hospital, outpatient, and nursing home files and was augmented with linkage to death certificates[1;3] and a statewide hospital discharge database. The linkages used all available identifiers.

The cohort included new episodes of therapy for the study drugs during the period 1/1/1999 through 12/31/2012. To enter the cohort, patients had to meet study inclusion/exclusion criteria (Appendix Table 1) on the day the prescription was filled (t_0). Appendix Table 2 shows the numbers of qualifying episodes of long-acting opioids and control drugs at each step.

Criterion 2 identifies the age range of study interest.

Criteria 3-5 are related to the availability in the Medicaid files of the medical encounters needed to define exposure to study drugs and comorbidity. In addition to requiring that cohort members have Medicaid enrollment with pharmacy benefits for at least one year (criteria 3-4), we also require medical care utilization during that year (criterion 5). Given that most study covariates were ascertained from medical care encounters, this assured some degree of medical surveillance.

Criteria 6-8 are designed to identify a population in which the occurrence of out-of-hospital death should be infrequent. This excludes persons with cancer and other life-threatening somatic illnesses, evidence of hospice or other end-of-life care, in long-term care, or recently discharged from the hospital.

Criterion 9 is the new episode of therapy requirement. Criterion 10 further restricts this group to those with diagnosed chronic pain in the past 90 days.

Criterion 11 excludes patients with unusually high starting doses of long-acting opioids and analgesic anticonvulsants. Thus, we excluded the small number of persons with a long-acting opioid starting daily dose of >180 mg morphine-equivalents, considered unusually high,[4] and with an anticonvulsant starting daily dose >1800 mg gabapentin, the approximate equivalent given the distribution of doses in the study cohort. No further exclusion was necessary for cyclic antidepressants, given that criterion 1 required daily doses of ≤150 mg of amitriptyline equivalents, given consistent recommendations that the higher doses appropriate for mood disorders are inappropriate for chronic pain.[5-8]

Patients who left the cohort could reenter, although this was infrequent. Each group included 22,912 episodes of therapy. In the long-acting opioid group, there were 20,405 unique patients; in the control medication group there were 21,053 unique patients.

Appendix Table 1. Criteria for new user episode of study drug use.

Criterion
1. **Study drug.** Filled prescription for a study drug and, with the exception of transdermal fentanyl, in an oral formulation. The class for which this prescription is filled is the *cohort entry class*. The prescription must be filled during the study period with at least one edited day of supply (§3). Let t_0 be the date of the prescription fill.
2. Age. Age 30 to 74 years on t_0. The lower age limit is present because death in children and young adults is rare. The upper limit is present because out-of-hospital death is less likely to be unexpected for persons 75 years of age or older.
3. **Enrollment.** Alive and enrolled in TennCare with date of birth and sex known on t_0 and enrolled for the period [t_0-364,t_0-1] (allowing gaps of up to 7 days).
4. **Pharmacy benefit.** Enrolled on t_0 in a category that provides full pharmacy benefits. Note for 2006 this definition must take into account the fact that persons with Medicare enrollment (those 65 years of age or older or those with qualifying disability) no longer have Medicaid pharmacy benefits because they obtain medications through Medicare part D.
5. **Medical history.** At least one outpatient visit and one filled prescription in the period [t_0 -364, t_0-1], excluding lab claims, to assure that patients have had regular contact with medical care.
6. **Somatic illness/Drug abuse.** No serious somatic illness or recorded evidence of drug abuse in the period [t_0 -364, t_0]. Somatic illnesses are cancer, HIV, end-stage renal disease, primary pulmonary hypertension and other immediately life-threatening cardio-respiratory illness, multiple sclerosis and other serious neuromuscular disorders, life-threatening congenital anomalies (e.g., heart defects, sickle cell), feeding problems, and hospice or other end-of-life care. Drug abuse was defined as a recorded diagnosis consistent with substance abuse other than alcohol/nicotine, a procedure consistent with therapy for substance abuse, or a prescription for buprenorphine.
7. **Long-term care.** Not residing in a nursing home or other residential institution in the interval [t_0 -364, t_0], except for stays of <30 days following hospital discharge.
8. **Recent hospital.** Not in the hospital (day of admission through discharge) in the period [t_0 -29, t_0].
9. New user. For the period [t_0 -364, t_0-31], no other filled prescription for any drug in the cohort entry class (regardless of dose). We allow up to 31 days of prior use to account for persons starting drug on discharge from the hospital. No filled prescription in the period [t_0 -364, t_0] for any drug in the other study classes.
10. **Chronic pain indication.** A diagnosis of chronic pain in [t_0 -89, t_0].
11. Starting dose. Starting dose for long-acting opioids no more than 180 mg/day morphine-equivalents; for anticonvulsants no more than 1800 mg/day gabapentin-equivalents.
12. **Propensity-score matched.** Frequency-matched according to centile of the propensity score distribution for the long-acting opioid group

Appendix Table 2. Numbers of persons meeting study eligibility criteria.

Criterion	Long-acting opioids	Anticonvulsant/TCA
1. Study drug	135,310	583,291
2. Age	109,396	424,495
3. Enrollment	95,051	371,424
4. Pharmacy benefit	93,261	366,878
5. Medical history	92,681	363,326
6. Somatic illness/Drug abuse	63,923	308,212
7. Long-term care	62,378	303,761
8. Recent hospital	58,689	297,725
9. New user	28,279	193,474
10. Chronic pain indication	24,081	133,547
11. Starting dose	23,308	131,883
12. Propensity-score matched	22,912	22,912

2. Study Drugs: Opioids

Both study and non-study opioids are shown in Appendix Table 3.

Appendix Table 3. Study and nonstudy opioid analgesics[a], with clinical dose equivalents, generally from vonKorff.[9;10]

Drug	Morphine Equivalent Conversion Factor	Equianalgesic doses, mg or mcg/hr
Study opioids		
1. Morphine, SR	1.0	30
2. Oxycodone, CR	1.5	20
3. Fentanyl, transdermal	25μg/hr = 50mg morphine SR[a]	15mcg/hr
4. Methadone	3.0	10
Non-study opioids, other non-parenteral		
Butorphanol, intranasal	21.4	1.4
Codeine	0.15	200
Dihydrocodeine	0.25	120
Fentanyl, transmucosal	125	240mcg
Fentanyl, oral	300	100mcg
Hydrocodone	1.0	30
Hydromorphone	4.0	7.5
Levorphanol	11.0	2.7
Meperidine	0.1	300
Morphine, not SR	1.0	30
Oxycodone, not CR	1.5	20
Oxymorphone	3.0	10
Pentazocine	0.37	81
Propoxyphene HCL	0.23	130
Propoxyphene napsylate	0.15	200
Tapentadol	0.23	133
Tramadol	0.1	300

[a]These do not include the antitussive levopropoxyphene, cough preparations, tincture of opium (Paregoric, given to treat diarrhea), and hydrocodone in cough preparations, both tablet (e.g., Hycodan) and syrup/liquid. They also do not include buprenorphine, which we use as a marker for substance abuse treatment. Does not include parenteral drugs. Doses generally from vonKorff. Fentanyl doses are micrograms/hour.

3. Study Drugs: Other Drugs for Chronic Pain

The other drugs for chronic pain include certain analgesic anticonvulsants (Appendix Table 4) and the cyclic antidepressants (Appendix Table 5) in doses of ≤150 mg of amitriptyline or its equivalent.

Appendix Table 4. Study analgesic anticonvulsants.

Drug	Equivalent Dose
1 Gabapentin	900
2 Pregabalin	200
3 Carbamazepine	600

Appendix Table 5. Study cyclic antidepressants.

Drug	Equivalent Dose
1 Amitriptyline Hydrochloride	100
2 Desipramine	100
3 Doxepin Hydrochloride	100
4 Imipramine	100
5 Nortriptyline Hydrochloride	50
6 Protriptyline Hydrochloride	15
7 Trimipramine Maleate	100
8 Amoxapine	100
9 Maprotiline Hydrochloride	100
10 Clomipramine HCL	100

4. Distribution of Study Covariates in Matched Cohort

The distribution of study covariates at the beginning of follow-up according to study drug group is shown in Appendix Table 6. All values are proportions unless otherwise stated, and, unless otherwise stated, reflect medical care encounters or prescriptions in the past year.

Appendix Table 6. Distribution of all study covariates at cohort entry according to study group.

Covariate		Control (N = 22,912)	Long-Acting Opioid (N = 22,912)
1	Sex female	59.8%	60.0%
2	White race (self-reported to Medicaid)	81.9%	81.6%
3	Age at baseline, years	47.9	47.9
4	Standard Metropolitan Statistical Area	49.4%	49.4%
5	Medicaid enrollment disabled	58.6%	58.4%
6	Year: 1999	3.0%	3.2%
7	Year:2000	7.6%	7.5%
8	Year:2001	10.9%	11.0%
9	Year:2002	12.2%	12.7%
10	Year:2003	14.3%	14.2%
11	Year:2004	13.6%	13.7%
12	Year:2005	10.3%	10.6%
13	Year:2006	4.4%	4.5%
14	Year:2007	4.7%	4.7%
15	Year:2008	3.9%	3.8%
16	Year:2009	2.9%	2.7%
17	Year:2010	3.6%	3.5%
18	Year:2011	3.9%	3.5%
19	Year:2012	4.8%	4.4%
20	Back pain past 90 days	75.7%	74.5%
21	Other musculoskeletal pain past 90 days	63.7%	63.3%
22	Abdominal pain past 90 days	17.9%	17.9%
23	Headache past 90 days	11.6%	12.1%
24	Other neurologic pain past 90 days	16.3%	16.8%
25	Persistent back pain	50.2%	50.2%
26	Persistent other musculoskeletal pain	35.9%	35.7%
27	Persistent abdominal pain	5.0%	4.8%
28	Persistent headache	3.4%	3.6%
29	Persistent other musculoskeletal pain	4.9%	5.1%
30	Rheumatoid arthritis/other inflammatory arthropathy	8.8%	8.8%
31	Current short-acting opioid, <=15mg morphine equivalents	12.3%	11.9%
32	Current short-acting opioid, 16-30mg morphine equivalents	19.6%	18.4%
33	Current short-acting opioid, 31-60mg morphine equivalents	23.2%	22.6%
34	Current short-acting opioid, >60mg morphine equivalents	13.1%	14.1%
35	Short-acting opioid, any	96.9%	96.3%
36	Short-acting opioid, 91-180 days use prior year	18.9%	18.4%
37	Short-acting opioid, 181-270 days use prior year	18.3%	17.6%

38	Short-acting opioid, >270 days use prior year	26.3%	27.0%
39	Skeletal muscle relaxant, any	62.8%	62.7%
40	Skeletal muscle relaxant, >270 days use prior year	8.2%	8.6%
41	Non-steroidal antiinflammatory drug, any	69.9%	69.3%
42	Non-steroidal antiinflammatory drug, >180 days use prior year	14.6%	14.6%
43	Corticosteroid, any	3.5%	3.7%
44	DMARD, any	4.6%	4.6%
45	Other analgesic, any	14.8%	15.0%
46	Benzodiazepine, any	51.4%	52.3%
47	Benzodiazepine, current, <5mg diazepam	2.7%	2.8%
48	Benzodiazepine, current, 6-9mg	7.5%	7.5%
49	Benzodiazepine, current, 10-19mg	11.2%	11.7%
50	Benzodiazepine, current, 20+mg	11.9%	12.9%
51	Benzodiazepine, 90-180 days use prior year	6.9%	7.0%
52	Benzodiazepine, 181-270 days use prior year	7.0%	7.0%
53	Benzodiazepine, >270 days use prior year	20.9%	21.6%
54	Antipsychotic, any	6.8%	6.8%
55	SSRI/SNRI	45.2%	45.5%
56	Trazodone	13.0%	13.1%
57	Other antidepressant	14.7%	15.2%
58	Other GABA agonist	15.4%	15.4%
59	Hydroxyzine	14.9%	14.7%
60	Other anxiolytic	4.2%	4.1%
61	Schizophrenia or other psychosis	2.4%	2.4%
62	Bipolar	6.8%	6.7%
63	Depression	14.6%	14.4%
64	Other affective disorder	21.8%	21.8%
65	Sleep disorder	12.4%	12.8%
66	Panic disorder	4.9%	5.1%
67	Anxiety disorder	22.9%	22.8%
68	ACE inhibitor	29.0%	29.0%
69	Angiotensin receptor blocker	7.4%	7.6%
70	Anticoagulant	5.2%	5.0%
71	Aspirin	9.2%	9.1%
72	Beta blocker	20.8%	21.1%
73	Calcium channel blocker	19.2%	19.5%
74	Digoxin	2.2%	2.2%
75	Loop diuretic	16.7%	16.6%
76	Other diuretic	22.0%	22.5%
77	Insulin	6.2%	6.1%
78	Oral hypoglycemic	13.6%	13.7%
79	Statin	25.0%	25.1%
80	Fibrate	5.5%	5.6%
81	Nitrate	10.3%	10.3%

82	Platelet inhibitor	5.6%	5.4%
83	New cardiovascular medication start	7.6%	7.6%
84	Serious coronary heart disease	6.1%	6.1%
85	Cardiac valve disorder	2.8%	2.9%
86	Arrhythmia	6.3%	6.3%
87	Congestive heart failure	5.4%	5.4%
88	Cerebrovascular disorder	5.4%	5.3%
89	Peripheral vascular disease	4.0%	3.9%
90	Diabetes	18.2%	18.4%
91	Hypertension	42.7%	42.8%
92	Hyperlipidemia	20.8%	20.9%
93	Other cardiovascular	11.4%	11.1%
94	Obesity	5.3%	5.3%
95	Smoking	22.8%	22.7%
96	Diabetes complications	5.6%	5.6%
97	Diabetes poor control	7.2%	7.0%
98	Diabetes hospitalization	6.0%	5.8%
99	New cardiovascular diagnosis	8.2%	8.2%
100	Unintentional fall	11.6%	11.6%
101	Wheelchair or walker	5.4%	5.5%
102	Incontinence	1.9%	2.0%
103	Other frailty	2.4%	2.5%
104	Home health care	2.1%	2.0%
105	Beta agonist	31.1%	31.4%
106	Other bronchodilator	17.2%	17.5%
107	COPD	20.0%	20.1%
108	Asthma	10.9%	11.3%
109	Home oxygen	6.1%	6.0%
110	Anticonvulsant	13.6%	13.7%
111	Seizure disorder	4.2%	4.3%
112	Hospitalization in [t0-90,t0-31]	4.7%	4.7%
113	Hospitalization in [t0-365,t0-91]	12.7%	12.8%
114	ED past 30 days	15.7%	15.3%
115	Cardiovascular outpatient visit past year	68.5%	68.5%
116	Outpatient visits past year: 6-20	51.7%	51.7%
117	Outpatient visits past year: 21-60	34.3%	34.1%
118	Outpatient visits past year: >60	1.8%	1.8%
119	Injury inpatient stay	2.5%	2.5%
120	Injury ED visit	33.3%	32.9%
121	Injury outpatient visit	41.2%	41.1%
122	Overdose inpatient stay/ED visit	2.8%	2.8%

5. End points

The study end point was any death during follow-up, classified according to whether or not the death was out-of-hospital or in-hospital. All deaths were identified by linking the Medicaid enrollment file with computerized death certificate files provided by the state health department that included the final underlying cause of death.[1;3]

Out-of-hospital deaths. An *out-of-hospital death* was one that occurred on a follow-up day during which the patient was out of the hospital. We considered these separately given that such deaths in a cohort that excludes persons with identified life-threatening diseases are less likely to be related to pre-existing illnesses and thus may better reflect adverse medication effects. Out-of-hospital deaths were further classified as *unintentional overdose deaths*, *cardiovascular deaths*, *respiratory deaths*, *other injury deaths*, and *other deaths*. This classification was based on the underlying cause of death, as multiple cause death certificate files were not available for all study years. Appendix Table 7 shows the definitions for each category.

Appendix Table 7. Codes for study causes of death.

ICD-10 Code	Rubric
Unintentional Medication Overdose Death	
X40-X44	Unintentional poisoning
Y40-Y57	Adverse effects of medications
Y10-Y14	Undetermined intent poisoning
Cardiovascular Death	
E10, E11, E13, E14	Diabetes[a]
I00-I02	Acute rheumatic fever
I05-I09	Chronic rheumatic heart disease
I10-I15	Hypertensive diseases
I20-I25	Ischemic heart disease
I26-I28	Diseases of pulmonary circulation
I30-I52	Other forms of heart disease
I60-I69	Cerebrovascular disease
I70-I79	Diseases of arteries, arterioles, and capillaries
I80-I89	Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified
I95-I99	Other and unspecified disorders of the circulatory system
R96.0	Instantaneous death
R96.1	Death in <24 hours
R98	Unattended death
R99	Unknown cause
Respiratory Death	
Jxx.x	Respiratory illnesses
R09.2	Respiratory arrest
W78	Aspiration
Other Injury Deaths	
Vxx.x, Wxx.x, Xxx.x, Yxx.x, if not unintentional medication overdose death	
Other Deaths	
All other causes of death	

[a]Excludes pregnancy-related diabetes.

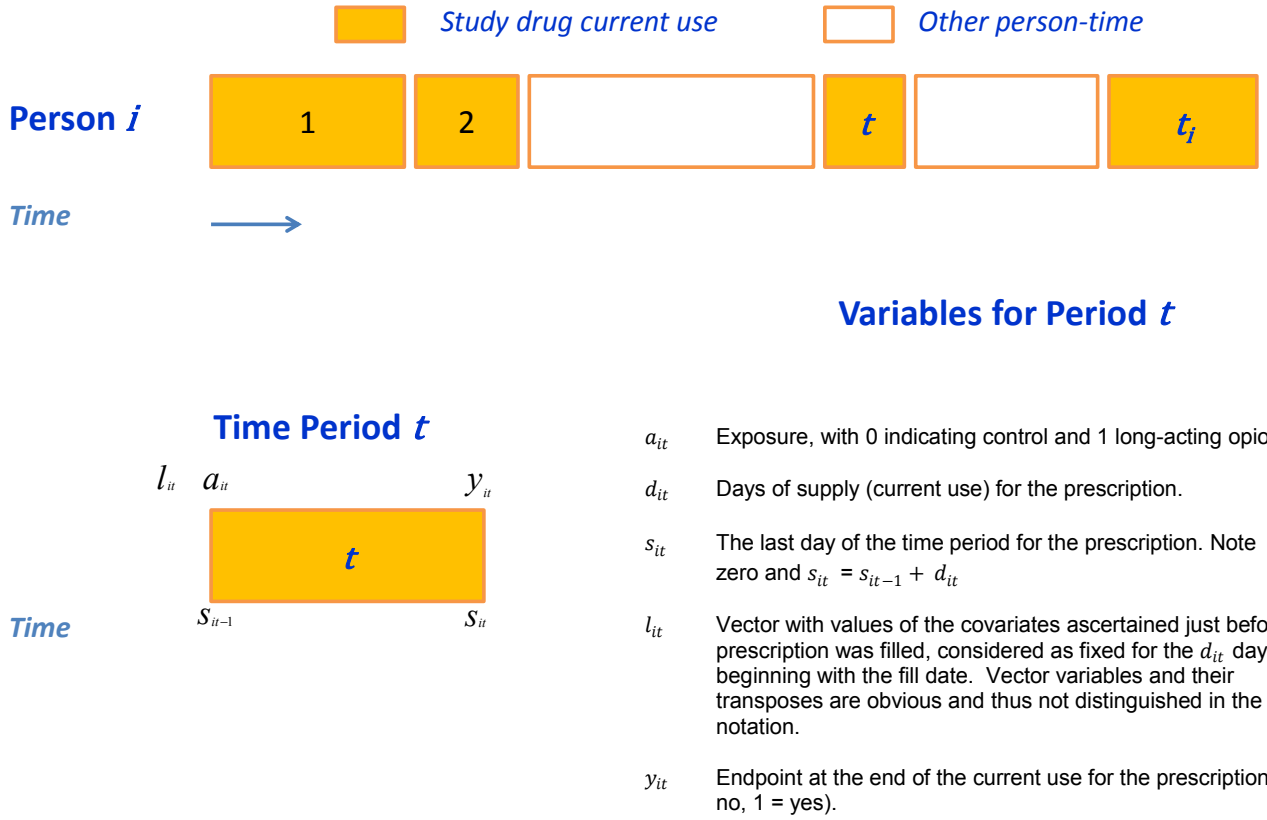
In-hospital deaths. In-hospital deaths were included because it is possible that the harms of one class of medication might be reflected in out-of-hospital deaths, whereas the other classes might confer increased risk of an ultimately fatal hospitalization. An in-hospital death is defined as one that occurred within 30 days of hospital admission, which assures that patients who enter the hospital but are discharged to hospice or SNF are counted as a death. This definition also excludes deaths after the small number of long-term hospitalizations.

6. Statistical Analysis

This section provides more details regarding the statistical analysis and describes certain sensitivity analyses.

1. Setting and Notation

Appendix Figure 1 depicts the setting and variable notation. For each person[a] i in the cohort, study follow-up consists only of periods of current use of study drugs, with each period corresponding to a filled prescription. Follow-up thus is divided into a series of intervals $(s_{it-1}, s_{it}]$, each consisting of the period at risk (t) for a single filled prescription. Person-time during intervals off drug is not considered.



a_{it}	Exposure, with 0 indicating control and 1 long-acting opioid.
d_{it}	Days of supply (current use) for the prescription.
s_{it}	The last day of the time period for the prescription. Note s_{i0} is zero and $s_{it} = s_{it-1} + d_{it}$
l_{it}	Vector with values of the covariates ascertained just before the prescription was filled, considered as fixed for the d_{it} days beginning with the fill date. Vector variables and their transposes are obvious and thus not distinguished in the notation.
y_{it}	Endpoint at the end of the current use for the prescription (0 = no, 1 = yes).

Appendix Figure 1 Setting and notation.

[a] Corresponds to a new episode of therapy.

2. Statistical Model

In all analyses, we fit a proportional hazards model for the risk of death during the s_i total days of current use during followup of study drug a_i (0=control, 1=long-acting opioid) for subject i. The hazard of medication toxicity death on day s in (0, s_i] given study drug a_{is} and covariates l_{is} was

$$\lambda(s \mid a_{is}, l_{is}) = \lambda_0(s) * exp(\beta_1 * a_{is} + \beta_2 * l_{is})$$

with

$\lambda_0(s)$	the baseline hazard;
β_1	log of the hazard ratio (HR) for current use of long-acting opioids versus control drugs;
β_2	vector of log HRs for the covariates.

The time scale for this proportional hazards model is cumulative days of current use of the study medication. Thus, the risk set for each day on which an event occurs consists of patients with the same duration of therapy as that for the patient who experienced the event.

The time-dependent covariates coefficients are estimated from PROC SAS PHREG, using the counting process syntax, which accommodates non-proportional hazards.

In the primary analysis, we stratify by deciles of the baseline propensity score, via the PHREG STRATA statement, an efficient way of controlling for a variable for which is not of direct interest. The time-dependent variables are age and calendar year. Because only current use is included in followup, the study medication variable is not time-dependent.

3. Time-Dependent Propensity Score

We conducted a sensitivity analysis with a time-dependent propensity score,[11] which checked for imbalances between the study groups that developed during follow-up. In this analysis, the propensity score was calculated from all study covariates and was updated on each prescription fill. The HR for all deaths was 1.71 (1.31-2.23), similar to that for the primary analysis.

4. Analysis by Duration and Dose.

In the analyses by duration and dose, each of these were time-dependent variables, calculated according to values at the beginning of each prescription interval. Duration was defined as cumulative days of current use just prior to the filling of the prescription. Dose was that for the prescription just dispensed.

To control for confounding in this analysis, a time-dependent disease risk score was estimated. Covariates could change on each date of a study drug prescription fill.

The disease risk score, often described as the prognostic analogue of the propensity score,[12] is the risk of the study endpoint as a function of the covariates, given the reference category for the exposure.[13-15] The disease risk score is particularly useful for non-dichotomous exposure categories.[13-15]

The disease risk score was calculated from a proportional hazards model estimating the coefficients for all study covariates, allowing them to change with each prescription fill. Given the parameter estimates for this model, we calculate the linear predictor $\beta_2 * l_{is}$, which is the predicted value given control drug exposure, and classify cohort followup into the 20 quantiles according to this score. These quantiles reflect risk under the assumption of no opioid use, assuming no interaction between the exposure and the covariates. Although it is

possible to estimate the score in the subgroup not using long-acting opioids, experience suggests that in the absence of effect modification, the estimate is better if the entire cohort is used.[15]

The resulting disease risk score ranged from 0 (lowest risk 5% of cohort) to 19 (highest risk 5% of cohort).

7. Results: Out-of-Hospital Cardiovascular Deaths

Appendix Table 8 shows the occurrence of out-of-hospital cardiovascular deaths according to specific subcategories of the death certificate underlying cause of death. Given the small numbers, all incidences are unadjusted.

Appendix Table 8. Incidence of out-of-hospital cardiovascular deaths according to specific underlying cause of death.

	Anticonvulsants/Cyclic Antidepressants (8,066 PY)		**Long-Acting Opioids (11,070 PY)**	
	Deaths	*Rate/10,000*	*Deaths*	*Rate/10,000*
Diabetes	4	5.0	4	3.6
Hypertension	3	3.7	6	5.4
Myocardial infarction	15	18.6	27	24.4
Other Coronary Artery Disease `	12	14.9	24	21.7
Cardiac Arrest	0	0.0	2	1.8
Heart Failure	1	1.2	3	2.7
Cerebrovascular	0	0.0	3	2.7
Other	0	0.0	3	2.7
Unknown cause death	1	1.2	7	6.3

8. Sensitivity Analysis: Cardiovascular Death Misclassification

1. Objectives

The risk of out-of-hospital cardiovascular deaths was increased for long-acting opioid users, with an HR of 1.65 (1.10-2.46). However, the definition of cardiovascular death was based upon the death certificate underlying cause of death. Thus, one explanation for this finding is that it results from differential misclassification of deaths coded as due to cardiovascular causes. For example, if overdose deaths among long-acting opioid users were miscoded as cardiovascular deaths, the effect would be to exaggerate their risk of cardiovascular death.

This sensitivity analysis assesses the possible effects of differential misclassification of out-of-hospital cardiovascular deaths. It is based on a convenience sample of deaths in the long-acting opioid users for which we obtained and adjudicated terminal medical records for out-of-hospital deaths, including emergency medical services, emergency department visits, and autopsy reports.

2. Convenience Sample

The sensitivity analysis sample came from a previous retrospective cohort study that compared out-of-hospital mortality for users of methadone versus morphine SR.[16] The cohort for that study consisted of patients prescribed these long-acting opioids between 1997 and 2009 and thus included some patients in the

present study. As part of the methadone/morphine SR study, medical records were obtained for study deaths when these were available and were adjudicated to determine if they met the sudden cardiac death criteria of the American College of Cardiology/American Heart Association (ACC/AHA) definitions for cardiovascular clinical trial endpoints.[17] There were 50 of the methadone/morphine SR study deaths for which medical records were available that occurred among long-acting opioid users in the current study (Appendix Table 9). These deaths constituted the convenience sample and thus were adjudicated to evaluate misclassification.

Appendix Table 9. Out-of-hospital deaths according to cause of death and inclusion in the convenience sample for which medical records were available.

	All Study Out-of-Hospital Deaths	Deaths in Convenience Sample
	N	N
All deaths	154	50
Death certificate cause of death		
Unintentional overdose	34	16
Cardiovascular	79	23
Other out-of-hospital	41	11

3. Estimating Misclassification Effect.

The effect of cardiovascular death misclassification for the long-acting opioid users can be estimated from the methadone/morphine SR sample. Because there was no comparable sample of deaths for the control drug users, we assumed a conservative scenario of no misclassification of control cardiovascular deaths.

The HR for cardiovascular deaths is approximately equal to the unadjusted incidence rate-ratio (IRR). That is,

$$HR \cong I_1 \,/\, I_0$$

where I_1 and I_0 are the respective incidences of cardiovascular deaths in the opioid and control groups. Note

$$I_1 = N_1 \,/\, L_1$$

where N_1 is the number of cardiovascular deaths and L_1 the person-time at risk for the opioid group. Note

$$N_1 = p * T_1$$

where T_1 is the total number of deaths in the opioid group and p is the proportion of those deaths that are cardiovascular. Let

$$N'_1$$

be the observed number of cardiovascular deaths (includes the misclassified deaths) and let

$$p' = N'_1/T_1$$

be the observed proportion of cardiovascular deaths.

Then,

$$N_1 = \left(\frac{p}{p'}\right) * N'_1$$

Given no misclassification of cardiovascular deaths in the control group, the true IRR for cardiovascular disease is the observed IRR multiplied by $\left(\frac{p}{p'}\right)$; a similar correction can be applied to the HR.

The effect of misclassification on the HR confidence intervals can be estimated analogously. The standard error of the ln(IRR) is

$$s = \sqrt{\frac{1}{N_1} + \frac{1}{N_0}}$$

where N_0 is the number of cardiovascular deaths in the control group. The effect of misclassification on the standard error can be estimated by s/s', the ratio of the standard error adjusted for known misclassification to the observed standard error. For example, if the observed number of cardiovascular deaths is larger than the true number ($N'_1 > N_1$), then the analysis with misclassification will underestimate the standard error ($s' < s$) and confidence intervals will be too narrow. Calculating N_1 as above, we can then estimate s and multiply the standard error of ln(HR) by s/s' to obtain confidence intervals adjusted for the effect of misclassification.

4. Adjudication

The adjudication required criteria for determining the likelihood of whether or not an unexpected out-of-hospital death was due to a cardiac cause. The data available for performing the adjudication included terminal EMS and ED records, medical examiner reports, autopsy findings, and records from services evaluating suitability for organ donation.

For cardiovascular deaths, the ACC/AHA cardiovascular endpoint definitions for clinical trials[17] are a widely accepted standard. For unexpected out-of-hospital deaths, the most common cardiovascular death according to these criteria is sudden cardiac death, which can be determined based on reports of the patient's state of health in the preceding 24 hours, the terminal medical records, and the autopsy findings. On occasion, autopsy data support another cardiovascular cause such as myocardial infarction.

However, assigning an unintentional overdose cause of death is more complex. [18;19] Absent a massive overdose, drug levels may be inconclusive, given the large variation in opioid tolerance and postmortem changes in drug distribution.[18] Thus, given postmortem data, it may be difficult to distinguish cardiac deaths from overdose deaths.[19]

Given these factors, we adopted a conservative adjudication process that would be likely to overestimate the probability of cardiovascular death misclassification. We also tested the effects of varying the adjudication criteria.

The fundamental premise was that we would not overrule a death certificate cause of death indicating overdose unless there was compelling evidence to the contrary. In order to be considered as a cardiovascular death, a death coded as due to overdose had to occur within 1 hour of symptom onset, with no evidence to support an overdose death in this short time frame. For such deaths, we applied ACC/AHA criteria to determine cardiovascular death status. This definition was conservative as several of the other overdose deaths met ACC/AHA cardiovascular death criteria, but we could not unequivocally rule out an unintentional overdose.

We classified deaths not coded as due to overdose as probable cardiovascular deaths if either of two conditions were met:

a. The death met the ACC/AHA criteria for cardiovascular death;
b. The death did not meet the ACC/AHA criteria but was consistent with a cardiovascular death. For these cases we required that the death certificate indicate a cardiovascular death and that the terminal records be consistent with a cardiovascular cause. For example, one death was coded as due to deep vein thrombosis/pulmonary embolus (DVT/PE) with the patient seen in usual state of health less than 24 hours prior to the death. This did not meet the ACC/AHA criteria for a sudden cardiac death, but, given that there was no evidence of another cause of death (including overdose), we considered the death as due to DVT/PE (a cardiovascular cause of death), even though there was no confirmatory autopsy finding.

We performed two analyses that considered alternative criteria. The first classified deaths that did not strictly meet the ACC/AHA criteria as non-cardiovascular.

The second included possible cardiovascular deaths. These were deaths for which cardiovascular conditions were mentioned on the death certificate but terminal medical care records were inadequate to rule out a non-cardiovascular cause.

Adjudications were performed by the entire group of investigators. All decisions were unanimous.

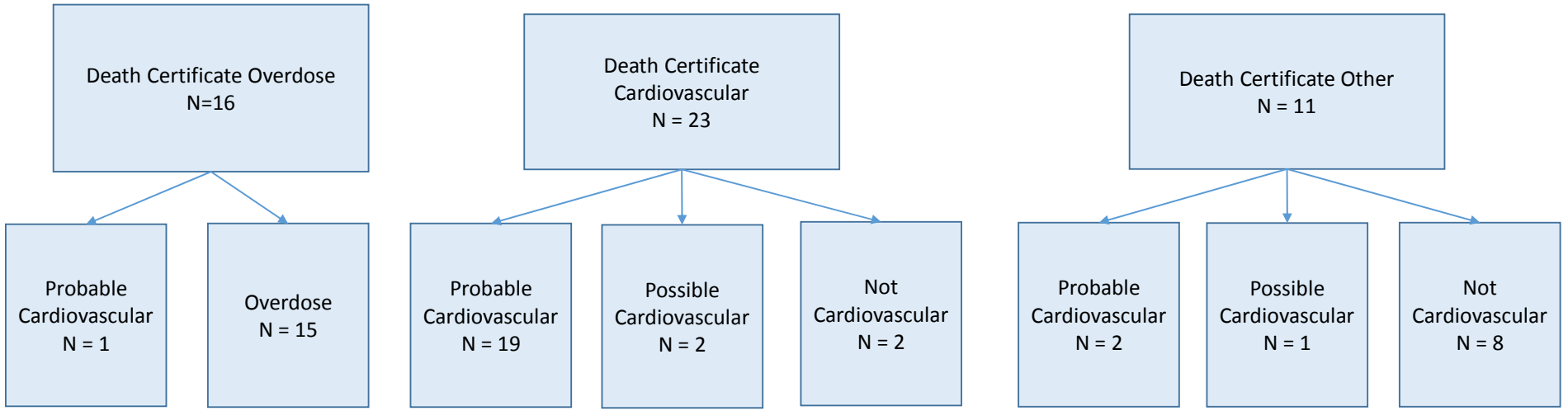
5. Results

Appendix Figure 2 shows the results of the adjudication. According to the death certificate, the basis of the analysis presented in the MS, 23/50 or 46% of out-of-hospital deaths were cardiovascular deaths. After adjudication of terminal medical records, 22 deaths were classified as probable cardiovascular. These included 1 of the 16 deaths coded on the death certificate as due to overdose, 19 of the 23 deaths coded as cardiovascular, and 2 of the 11 other deaths. Thus 22/50, or 44% of out-of-hospital deaths were adjudicated as probable cardiovascular, which would reduce the observed HR from 1.65 (1.10-2.46) to an estimated 1.58 (1.05-2.36).

Of the 22 deaths we adjudicated as probable cardiovascular deaths, 3 did not meet the strict ACC/AHA criteria. For two of these deaths, this was due to uncertainty regarding timing. For example, if the medical record noted the patient was in the usual state of health “the preceding day”, we could not unambiguously infer death within 24 hours of symptom onset. As mentioned above, for one of these deaths the terminal records supported DVT/PE but no autopsy findings were available. If these three deaths were considered non-cardiovascular, then 19/50 or 38% of out-of-hospital deaths would be classified as cardiovascular, which would result in an estimated HR of 1.36 (0.90-2.06).

There were 3 deaths that met our criteria for possible cardiovascular deaths. If these were considered cardiovascular deaths, then 25/50 or 50% of out-of-hospital deaths would be classified as cardiovascular, which would result in an estimated HR of 1.79 (1.21-2.66).

This analysis provides evidence that, even under conservative assumptions, the elevated HR for cardiovascular deaths for long-acting opioid users is not explained by cardiovascular death misclassification.



Appendix Figure 2 Adjudication results.

6. Limitations

The adjudication process had several limitations. There were no deaths from the control group. However, we made the conservative assumption of no misclassification of control cardiovascular deaths. To the extent that such deaths also were misclassified, the sensitivity analysis findings would underestimate the cardiovascular death HR.

The convenience sample was not drawn at random. It did not include all long-acting opioids nor did it encompass the entire study time period.

The death certificate underlying cause of death was considered in adjudication process. However, this was conservative in that we did not reclassify a death coded as due to unintentional overdose unless there was compelling evidence to the contrary.

9. References

(1) Ray WA, Griffin MR. Use of Medicaid data for pharmacoepidemiology. *Am J Epidemiol* 1989;129:837-849.

(2) Ray WA. Population-based studies of adverse drug effects. *N Engl J Med* 2003;349:1592-1594.

(3) Piper JM, Ray WA, Griffin MR, Fought R, Daugherty JR, Mitchel E, Jr. Methodological issues in evaluating expanded Medicaid coverage for pregnant women. *Am J Epidemiol* 1990;132:561-571.

(4) Ballantyne JC, Mao J. Opioid therapy for chronic pain. *N Engl J Med* 2003;349:1943-1953.

(5) Carragee EJ. Clinical practice. Persistent low back pain. *N Engl J Med* 2005;352:1891-1898.

(6) Chou R, Turner JA, Devine EB et al. The effectiveness and risks of long-term opioid therapy for chronic pain: a systematic review for a National Institutes of Health Pathways to Prevention Workshop. *Ann Intern Med* 2015;162:276-286.

(7) Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH et al. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 14, 162-173. 2015.

(8) Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev* 2012;12:CD008242.

(9) Von Korff M, Saunders K, Ray GT et al. De facto long-term opioid therapy for noncancer pain. *Clin J Pain* 2008;24:521-527.

(10) Dunn KM, Saunders KW, Rutter CM et al. Opioid prescriptions for chronic pain and overdose. *Ann Intern Med* 2010;152:85-92.

(11) Ray WA, Liu Q, Shepherd BE. Performance of time-dependent propensity scores: a pharmacoepidemiology case study. *Pharmacoepidemiol Drug Saf* 2015;24:98-106.

(12) Hansen BB. The prognostic analogue of the propensity score. *Biometrika* 2008;95:481-488.

(13) Arbogast PG, Kaltenbach L, Ding H, Ray WA. Adjustment of multiple cardiovascular risk factors with a summary risk score. *Epidemiol* 2008;19:30-37.

(14) Arbogast PG, Ray WA. Use of disease risk scores in pharmacoepidemiologic studies. *Statistical Meth Med Res* 2009;18:67-80.

(15) Arbogast PG, Ray WA. Performance of disease risk scores, propensity scores, and traditional multivariable outcome regression in the presence of multiple confounders. *Am J Epi* 2011;174:613-620.

(16) Ray WA, Chung CP, Murray KT, Cooper WO, Hall K, Stein CM. Out-of-hospital mortality among patients receiving methadone for noncancer pain. *JAMA Intern Med* 2015;175:420-427.

(17) Hicks KA, Tcheng JE, Bozkurt B et al. 2014 ACC/AHA key data elements and definitins for cardiovascular endpoint events in clinical trials. *JACC* 2015;66:403-469.

(18) Letsky MC, Zumwalt RE, Seifert SA, Benson BE. Cause of death conundrum with methadone use. A case report. *Am J Forensic Med Pathol* 2011;32:193-196.

(19) Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MCP. QTc interval screening in methadone treatment. *Ann Intern Med* 2009;150:387-395.